Body Fat Distribution and Hyperinsulinemia as Risk Factors for Diabetes and Cardiovascular Disease

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Differences in body fat distribution between diabetics and nondiabetics have been recognized for several decades; diabetics have a more centralized or upper body fat pattern than nondiabetics. Recently, attention has focused on fat patterning and also on hyperinsulinemia as possible risk factors for cardiovascular disease, as well. The case for insulin as a cardiovascular risk factor is bolstered by theoretical considerations related to its possibly atherogenic effects on serum and arterial wall lipids. Empirical evidence for fat patterning and hyperinsulinemia as cardiovascular risk factors rests on six prospective epidemiologic studies, three on fat patterning and three on insulin. Although provocative, none of these studies can be regarded as definitive. In none was a dose-response effect demonstrated, and there are various inconsistencies within and across the studies. Moreover, in none of the studies were hyperinsulinemia and fat patterning evaluated simultaneously. This is of particular importance in view of the well-documented interrelationships between these two variables. For example, insulin resistance and hyperinsulinemia have been found to be greater in women with upper body obesity compared to women with lower body obesity of equivalent degree. Considerable progress has been made recently in understanding the mechanisms of the differential metabolic effects of these two types of obesity. The extent to which fat patterning and hyperinsulinemia are genetic or acquired has received relatively little attention. Further research on this question is warranted since elucidation of any environmental influences on these variables might suggest new clinical and public health control measures.

(Arteriosclerosis 6:123-130, March/April 1986)
predicting model. Similarly, plasma triglyceride concentration typically "drops out" of multivariate models when variables with which it is correlated (e.g., obesity, HDL, etc.) are included. But this does not rule out the possibility that very low density lipoprotein (VLDL), the principal triglyceride-bearing lipoprotein in the fasting state, is itself atherogenic. A more technical discussion on the interpretation of risk factors in a multivariate context can be found in a recent publication by Abbott and Carroll and related correspondence.

In the case of obesity, another important consideration relates to the measurement problem. Obesity may be defined as an excess of body fat. But body fat as such is never directly measured in epidemiologic studies. Instead, it is invariably assessed indirectly by either weight-height indices or skin-fold measurements, or both. The former confounds body fat with other body compartments including muscle and skeletal mass, and the latter considers only subcutaneous fat at specified locations on the body. Thus, skinfolds do not even provide a global measure of adiposity. Moreover, the relationship between one or a combination of skinfold measurements and total body fat could well vary from individual to individual, depending on the distribution of body fat. Thus, a skinfold of a given thickness at a given site could be associated with different amounts of total body fat in different individuals. On the other hand, skinfolds are a principal method for assessing fat patterning, which is a main topic to be discussed in this review.

Glucose concentration has theoretical limitations as a potential cardiovascular risk factor stemming from the fact that it is subject to negative feedback control. As blood glucose rises, insulin secretion is stimulated which acts to blunt or reverse its further rise. Thus, under normal circumstances, glucose concentration is constrained to vary over a relatively narrow range which limits its ability to emerge as a consistent predictor variable. Insulin, by contrast, is not subject to this constraint and therefore has theoretical appeal as a risk factor. Other theoretical reasons for postulating insulin as a risk factor are summarized below.

Risk Factors

Body Fat Distribution

The importance of body fat distribution as a determinant of various metabolic disorders has been recognized for several decades. In 1956, Vague coined the terms "android" (upper body) and "gynoid" (lower body) obesity and noted that the former, though not the latter, was strongly associated with diabetes, atherosclerosis, and gout. In fact, the sex difference in body fat distribution had been recognized much earlier. The famous statue of Balzac by Rodin, shown in Figure 1, clearly indicates that the sculptor appreciated the typical male pattern with its powerful upper body and prominent abdomen. Recognition of the female pattern is of even greater antiquity. Prehistoric cave art contains many examples of so-called "Venus figures," thought to be fertility goddesses, an example of which is shown in Figure 2. The slender shoulders and upper body and the impressive accumulations of fat in the buttocks and thighs are apparent.

Although Vague emphasized the upper-lower body fat dichotomy, several subsequent workers chose to focus on the dichotomy between central (or truncal) and peripheral (or extremity) adiposity. With the introduction of a relatively simple index — the ratio of waist-to-hip circumference — the pendulum has again swung back to the upper-lower dichotomy. More recently, computerized tomography has made it possible to assess intra-abdominal fat. This fat depot is of particular interest since its strategic location within the portal circulation might confer on it a relatively unique role in adipose tissue metabolism. Recent reports indicate that the ratio of intra-abdominal to subcutaneous abdominal fat is greater in men than in women. In both sexes, this ratio is higher in individuals with predominantly upper body obesity than in those with predominantly lower body obesity.

Since most studies have relied on a single index of fat patterning, it is difficult to say which, if any, of the above indices is optimum. The pendulum has again swung back to the upper-lower dichotomy. More recently, computerized tomography has made it possible to assess intra-abdominal fat. This fat depot is of particular interest since its strategic location within the portal circulation might confer on it a relatively unique role in adipose tissue metabolism.

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A role for sex hormones in the distribution of body fat has been postulated for some time.13,15 Evidence for this concept has recently been presented by Evans et al.,29 who reported that women with primarily upper body fat localization (i.e., android) had increased free testosterone levels and decreased sex hormone-binding globulin compared to women of similar adiposity whose fat distribution was primarily lower body (i.e., gynoid).

The finding that diabetics tend to have more central or upper body fat than nondiabetics, while having similar or lesser degrees of peripheral or lower body fat, has been replicated many times.15,17,19,20,22-28 Another consistent finding has been that this phenomenon is more pronounced in women than in men.15,25,26,28 In the Kaiser population,15 diabetics and nondiabetics were matched by age, sex, height, and weight. Thus, in this study, the greater tendency toward central obesity in diabetics was manifested even when comparison was made with nondiabetics of equal body mass. In the Health and Nutrition Examination Survey (HANES-I), greater central adiposity was observed not only among diabetics,17 but among hypertensives as well.18 In a very large population (over 30,000 women members of TOPS Club, Incorporated, a voluntary weight reduction organization), Hartz et al.15,20 reported that, within defined strata of overall adiposity, there was a positive association between waist-to-hip ratio (higher values reflecting upper body fat predominance) and the prevalence of self-reports of several diseases including diabetes, hypertension, gallbladder disease, and menstrual disorders. A greater tendency toward upper body obesity in diabetics has also been reported in Mexican Americans from Starr County, Texas.25,26 In Tecumseh, Michigan, subscapular skinfold was found to be a somewhat better predictor of the future development of diabetes than triceps skinfold, although the results were not entirely consistent.27

There is some evidence that the effects of centralized adiposity may plateau at higher degrees of centrality. Haffner et al.28 examined this issue using as an index of centrality, the ratio of subscapular-to-triceps skinfold. Within defined strata of overall adiposity, there was a stepwise increase in diabetes prevalence in women as one moved from the lowest third to the highest third of the centrality distribution. In men, on the other hand, diabetes prevalence increased from the lowest third to the middle third, but then remained constant, or fell slightly from the middle third to the highest third of the centrality distribution. Since the centrality distribution is shifted to the right in men compared to women, these findings are compatible with the concept that the effects of centrality plateau at higher levels.

The mechanisms whereby body fat distribution might predispose to diabetes independently of overall adiposity have received considerable attention. There is evidence that subjects with predominantly upper body fat distribution are more insulin-resistant than equally obese subjects with predominantly lower body fat.29-31 Thus, for example, greater hyperinsulinemia, both fasting and in response to an oral glucose load, has been demonstrated in women with predominantly upper body obesity compared to equally obese women whose obesity is mainly of the lower body type.29,31 A more definitive technique for assessing insulin resistance in vivo involves determining steady-state plasma glucose (SSPG) concentrations during simultaneous intravenous infusion of somatostatin, glucose, and exogenous insulin.32 Using this technique, Evans et al.31 demonstrated a positive correlation between SSPGs (implying increasing degrees of insulin resistance) and waist-to-hip ratio. Multivariate analyses indicated that this effect was independent of the effect of overall obesity. Similar findings have been reported in former gestational diabetics with the use of intravenous glucose tolerance testing combined with computer-modeling, another sophisticated technique for assessing insulin resistance in vivo.33

It has also been shown that upper body obesity is associated primarily with fat cell hypertrophy, whereas lower body obesity is associated primarily with fat cell hyperplasia.26,30 Enlarged fat cells have been demonstrated to be relatively resistant to insulin action in vitro.34,35 Both an insulin receptor and a postsulin receptor defect have been implicated.36-38 However, since adipose depots account for only about 5% of total body glucose disposal,39,40 insulin resistance in this tissue alone should not, by itself, produce significant total body insulin resistance. Since skeletal muscle accounts for a substantially greater fraction of overall glucose disposal, efforts have been made to examine insulin resistance in this tissue. Using biopsies of the quadriceps muscle, Evans et al.41 measured the insulin responsiveness of glycogen synthetase and demonstrated reduced responsiveness in women with upper, as opposed to lower, body obesity. These workers also demon-
strated decreased insulin binding to monocytes from women with upper body obesity, implying a decreased number of insulin receptors in this type of obesity. Whether this insulin receptor defect involves other insulin-sensitive tissues as well is unknown, however.

The mechanism whereby upper body obesity produces insulin resistance in tissues other than adipose tissue (e.g., skeletal muscle) is poorly understood. A possible explanation relates to the observation that enlarged fat cells (characteristic of upper, but not lower, body obesity) exhibit increased basal lipolysis with resulting elevated blood levels of free fatty acids. It has been demonstrated that elevated free fatty acid levels diminish insulin sensitivity in both skeletal and heart muscle.

The results summarized above all seem to point to a central role for insulin resistance as the principal mediator of the adverse metabolic consequences of upper body obesity. Kissebah and colleagues, however, have offered an alternative formulation that derives principally from their observation that the fractional hepatic extraction of insulin is reduced to a greater extent in upper than in lower body obesity, thereby producing greater posthepatic delivery of insulin in the former type of obesity. These workers also reported that hepatic extraction of insulin is reduced in the presence of elevated levels of free testosterone and reduced levels of sex-hormone-binding globulin, both of which occur in upper, but not lower, body obesity. In addition, in situ liver perfusion studies in castrated male and female rats indicate that the dose of androgen required to suppress hepatic extraction of insulin was five to ten times higher in male rats than in female rats, suggesting greater sensitivity of the female liver to androgens. Given these observations, Kissebah and colleagues used multiple regression-pathway analysis to develop a model that assigns a central role to androgen excess, which is viewed as producing both upper body fat accumulation and decreased hepatic extraction of insulin. The latter then produces increased posthepatic delivery of insulin, hyperinsulinemia, and secondary insulin resistance, perhaps by down-regulation of insulin receptors.

The finding that hypertriglyceridemia is more strongly associated with central or upper body obesity than with peripheral or lower body obesity (equal degree has been reported many times, but not all) and that estrogen (unpublished observations) have shown that the higher triglyceride and lower HDL cholesterol levels in Mexican Americans compared to non-Hispanic whites, both of which persist after adjustment for overall adiposity and behavioral variables (cigarette and alcohol consumption, oral contraceptive and postmenopausal estrogen use), are markedly attenuated or eliminated once the more centralized adipose distribution of Mexican Americans is taken into account.

At least two mechanisms may explain the association between lipids and body fat distribution. As described above, upper body obesity is associated with hyperinsulinemia, and there is a considerable body of evidence indicating that hyperinsulinemia can stimulate hepatic production of very low density lipoprotein (VLDL) with resulting hypertriglyceridemia. In addition, the increased free fatty acid flux resulting both from insulin resistance and from the enhanced basal lipolysis of hypertrophied fat cells could also stimulate VLDL production by the liver, further contributing to hypertriglyceridemia.

A key limitation of the studies reviewed thus far is that they have all been cross-sectional and thus cannot distinguish between fat patterning as cause or as effect of diabetes. Recently, however, Ohlson et al. reported the results of a prospective epidemiologic study that indicated that upper body obesity as measured by waist-to-hip ratio (WHR) was predictive of the future development of diabetes. This effect was found to be independent of overall obesity. The role of fat patterning as a cardiovascular risk factor has also been examined in a prospective fashion. Two studies, both from Sweden, found that WHR was positively predictive of myocardial infarction, angina pectoris, stroke, and death from all causes. The effect of WHR was independent of other conventional cardiovascular risk factors in women, though not in men. In the Framingham Study, subscapular skinfold in both sexes was strongly predictive of a 22-year incidence of coronary heart disease (CHD) independent of overall obesity as measured by body mass index (BMI) and other conventional cardiovascular risk factors. In fact, in men, subscapular skinfold was more highly predictive than any of the other risk factors except for cholesterol. Abdominal skinfold and waist circumference were also independently predictive of CHD incidence in men, although not in women. Hip circumference was not measured in the Framingham Study, so that it was not possible to examine the effects of the WHR. Also of interest is the fact that, unlike the Swedish data, the effects of fat patterning in Framingham appeared to be stronger in men than in women.

Is the Pattern of Body Fat Distribution Genetic or Acquired?

Although overall obesity is recognized as having genetic determinants, it is clear that environmental factors (some combination of excess caloric intake, sedentary lifestyle, or both) also play an important role. A separate question is whether fat pattern, independent of overall obesity, is primarily genetic or acquired. Evidence for a genetic component has recently been presented by Boucraut, who reported that various indices of fat patterning were more highly correlated between biological siblings than adopted siblings and between monozygotic than dizygotic twins. These correlations were also higher between children and their natural parents than between children and foster parents. Monozygotic twins also resembled each other more than did dizygotic twins on several measures of adipose tissue metabolism such as basal and epinephrine-stimulated lipolysis, basal and insulin-stimulated glucose conversion to triglyceride, and lipoprotein lipase activity.

In the San Antonio Heart Study, we have been unable to demonstrate any relationship between the ratio of subscapular to triceps skinfold (centrality index) and any nutritional or other behavioral variables. These include total calories; percent of calories derived from protein, fat, carbohydrate, saturated fat, and linoleic acid; dietary cholesterol; polyunsaturated-to-saturated fat (P/S) ratio; exercise; alcohol consumption; cigarette smoking; and, in women, the use of oral contraceptives or postmenopausal estrogens (unpublished observations). In Mexican American women, however, the centrality index was significantly correlated with percent Native American genetic admixture (p < 0.001) (unpublished observations). This association, which was independent of BMI, might argue for a genetic basis for fat patterning, although it was observed only in women.

Lanska et al. found no effect of menopausal status on waist-to-hip ratio beyond that which could be explained by age. Only a negligible effect of parity was observed. Rebufé-Skriver et al. studied lipolysis rates and lipoprotein lipase activity in biopsies of femoral and abdominal adi-
pose tissue from nonpregnant, pregnant, and lactating women. These investigators found that the metabolic pattern in both pregnant and nonpregnant women favored fat deposition in the femoral region, whereas lactation stimulated fat mobilization from this depot. To date, no epidemiologic studies have been reported that examine possible differences in fat patterning between women who give a history of breast feeding vs those who do not.

Central or upper body obesity is generally thought to be associated with adult-onset rather than lifelong obesity, which might be used to argue for an environmental component. It appears, however, that this concept is based primarily on an inference from the fat cell hypertrophy/hyperplasia literature. Specifically, lifelong obesity has been associated with fat cell hyperplasia and adult-onset obesity with fat cell hypertrophy. Although this concept has been challenged, if one combines it with the observation that upper body obesity is predominantly hypertrophic and lower body obesity predominantly hyperplastic, one could perhaps infer that the former is acquired and the latter, inherited. Direct data on this topic, although limited, do not appear to support this concept, however. For example, neither Ashwell et al. nor Joes et al. found a relationship between fat patterning and either age of onset of obesity or weight gain in adult life. In the San Antonio Heart Study, the centrality index was positively correlated with weight gain after age 20 years in women, but not in men (Table 1). (Although the correlation in Mexican American men \( r = 0.054 \) was statistically significant at the 0.05 level, it was trivial in magnitude). After adjusting for age and BMI, however, these correlations were all close to zero (and, if anything, negative). Thus, our results also fail to support a relationship between fat patterning and age of onset of obesity.

Finally, the available evidence (which is not extensive) suggests that the pattern of body fat distribution is preserved in adults undergoing modest weight loss (less than 10 kg) although with greater weight loss the waist-to-hip ratio may decline.

Insulin

The role of circulating insulin concentration in the development of noninsulin-dependent diabetes (NIDDM) has been controversial with both insulin excess and insulin deficiency having been postulated as important antecedents. Early studies were mainly cross-sectional and thus did not clearly delineate the relevant time sequence. Prospective epidemiologic studies of NIDDM incidence, particularly studies in which insulin levels were measured at baseline, i.e., prior to disease onset, have been relatively few. In view of the relatively low rate of development of NIDDM in most populations, such studies have been carried out mainly in high risk populations. In both Pima Indians and South Pacific Islanders from Nauru (Sicree RA, Zimmet PZ, King HOM, Coventry JS. The insulin response as a predictor of glucose tolerance deterioration over six years among Nauruans with normal and impaired glucose tolerance; unpublished data) high circulating insulin concentrations were predictive of subsequent conversion from normal glucose tolerance to NIDDM. But among subjects categorized as having impaired glucose tolerance (IGT) at baseline, the opposite (i.e., low insulin concentrations) was predictive of subsequent conversion. Low plasma insulin levels were also predictive of conversion from IGT to NIDDM in a study from Japan.66

Although seemingly conflicting, these findings fit with the following formulation: the initial lesion leading to ultimate NIDDM is peripheral resistance to insulin action; to overcome this resistance, the pancreatic beta cells are compelled to hypersecrete insulin and hyperinsulinemia results; after many years of hypersecretion, the pancreatic beta cells eventually fail and insulin dependent diabetes result. The term "pancreatic exhaustion" has been used to describe this sequence of events.64 66 We have recently postulated67 that IGT is a heterogenous category containing both "high normals" and individuals who are either in transition to NIDDM or early ("test-negative") diabetes. According to this concept, the IGT category might contain many individuals in whom "pancreatic exhaustion" is already in progress. Thus, although IGT in general is associated with relatively high levels of circulating insulin,64 it is those IGT subjects who are undergoing pancreatic exhaustion and whose insulin levels are already dropping who are most likely to convert. In contrast, among individuals with normal glucose tolerance, insulin resistance is still compensated by beta cell hypersecretion, so that in these individuals, hyperinsulinemia, rather than low insulin levels, would be predictive of eventual conversion to NIDDM.

There is also evidence that hyperinsulinemia may be a risk factor for cardiovascular disease. The theoretical arguments have been summarized by Stouf.71-73 In addition to its effects on serum lipids and lipoproteins, summarized above, insulin has direct effects on the cells of the arterial wall that could be atherogenic. These include inhibition of lipolysis; stimulation of cholesterol, phospholipid, and triacylglyceride synthesis; and a mitogenic effect resulting in stimulation of smooth muscle proliferation.71-73

The role of insulin as a cardiovascular risk factor has been examined in three prospective, epidemiologic studies. In Helsinki policemen,74 blood glucose concentration was predictive of coronary heart disease (CHD), defined as CHD death and nonfatal myocardial infarction, in univariate analyses, but not after controlling for other cardiovascular risk factors (including age, systolic blood pressure, cholesterol, and smoking). In contrast, plasma insulin concentration was a significant independent risk factor for CHD even after adjusting for these other cardiovascular risk factors. Similar findings have been reported.

Table 1. Pearson Simple and Partial Correlations between Centrality Index (Ratio of Subscapular to Triceps Skinfold) and Weight Gain since Age 20 Years

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<tr>
<th>Metric</th>
<th>Mexican Americans</th>
<th>Non-Hispanic whites</th>
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<tbody>
<tr>
<td></td>
<td>Men ( n = 537 )</td>
<td>Women ( n = 707 )</td>
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<tr>
<td>Simple</td>
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<tr>
<td>( r )</td>
<td>0.054*</td>
<td>0.120†</td>
</tr>
<tr>
<td>Partial, controlling for age and log body mass index</td>
<td>-0.026</td>
<td>-0.067*</td>
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*p < 0.05; †p < 0.001.
should reduce this type of misclassification and the extent to which it accomplishes this goal can and should be quantified. Unfortunately, however, the types of data often presented in reports of prospective epidemiologic studies (e.g., model parameters, adjusted odds ratios) do not directly address the misclassification issue. It is even more difficult to compare misclassification rates across studies. Efforts should be made to present data from different studies in a standardized format that facilitates comparison of the misclassification rates associated with various models incorporating varying combinations of risk factors.

The development of innovative strategies for disease control hinges on the extent to which the risk factors in question are predominantly genetic or acquired. In the case of hyperinsulinemia and fat patterning, this question has received relatively little attention. Clinical and public health strategies aimed at controlling obesity have focused almost exclusively on overall obesity. If, as seems likely, the pattern of body fat deposition is an important determinant of health, it is necessary to identify any environmental factors that might influence this pattern. The elucidation of such factors could add important new dimensions to efforts designed to combat obesity. At the very least, it might be desirable to more vigorously advocate weight loss for those with central or upper body obesity than for those with other types of obesity. Clearly, additional research efforts on the genetic and environmental determinants of hyperinsulinemia and fat patterning are warranted.

References


Index Terms: obesity • fat patterning • hyperinsulinemia • diabetes • cardiovascular disease • epidemiology • genetics • insulin • race
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*Arterioscler Thromb Vasc Biol.* 1986;6:123-130
doi: 10.1161/01.ATV.6.2.123

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

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